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(56) Documents cited
GB 1423694
GB 1180233
GB 1075293
DE 2325036 A
DE 1965709 A
EP 0009688 A
Martindale's Extra Pharmacopeia, 27th Edn., (1977) p 832 r.h. column LL 14-16. Pharmaceutical Codex, 11th Edn., (1979) pp 149, 848 and 907. The Theory & Practice of Industrial Pharmacy, 2nd Edn., (1976) by Lachmann, Liebermann & Kanig, (Lea & Febiger) at p.333
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(54) **Palatable anthelmintic tablets for companion animals**

(57) Palatable anthelmintic compositions for animals, contain anthelmintically effective amounts of an N,N - dialkylpiperazine carboxamide, with or without a styrylpyridinium compound, in which the active ingredients are ionically bound to sulfonic cation exchange resins. The compositions also contain desiccated liver, brewers yeast, microcrystalline cellulose and stearic acid and may also contain sodium aluminium silicate or silicon dioxide.

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SPECIFICATION

Diethylcarbamazine resinate and styrylpyridinium resinate-diethylcarbamazine resinate edible anthelmintic tablets for companion animals

The present invention relates to palatable acidic resinate compositions which contain a styrylpyridinium compound and/or an N,N-dialkylpiperazine carboxamide and find utility as a papatable anthelmintic compositions for the treatment of helminthiasis in companion animals.

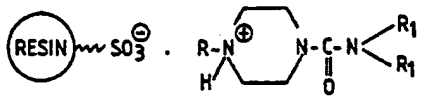
Styrylpyridinium compounds and methods for their preparation are disclosed in United States Patents 3,177,116 and 3,179,559, issued April 6, 1965 and April 20, 1965, respectively. Similarly, N,N-dialkylpiperazine carboxamides are disclosed in United States Patent 2,467,895, issued April 19, 1949. The above-identified compounds are known to be useful for combatting helminthiasis in domestic animals. They are said to be effective when administered by the oral route. Administration of both the N,N-dialkylpiperazine carboxamides and the styrylpyridinium halides, in the form of capsules, tablets and in the feed, is contemplated by the patentees. However, it has been found that the styrylpyridinium compounds are unpalatable when taken orally and the N,N-dialkylpiperazine carboxamides are only partially acceptable to companion animals when administered in a form in which the active compound is permitted to come in contact with the animals taste buds. Over the years, veterinarians have continually complained that the available tablets, pills or formulated compositions marketed for admixture of the styrylpyridinium halides with feeds is unsatisfactory and has resulted in the reluctance of the animals to ingest the medicated feed, tablets or pills. It would therefore be highly advantageous and most desirable if the above-named compounds could be rendered palatable without destroying their efficacy. Furthermore, it would be most advantageous if a palatable composition, containing a N,N-dialkylpiperazine carboxamide, alone or in combination with a styrylpyridinium compound such as a 1-methyl-2-(p-chlorostyryl) pyridinium salt, could be prepared in the form of a chewable tablet, pill, granulated product or the like.

Heretofore, it has been stated that, "both olfaction and taste are involved in canine food preferences". Thus, the use of split plate evaluations for preference are crucial in delineating olfactory medicated preferences. Actual consumption of an article is a function of combined odor and taste acceptability which is herein interpreted as palatability.

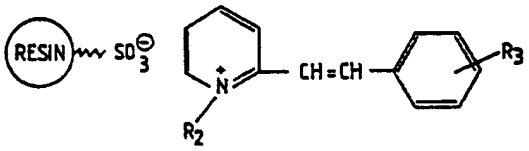
It is, therefore, an object of this invention to provide palatable, therepeutically effective compositions, containing a N,N-dialkylpiperazine carboxamide alone or in combination with a styrylpyridinium compound, useful for the treatment of helminthiasis in companion animals.

It is also an object of the present invention to provide methods for preparing diethylcarbamazine and/or styrylpyridinium compositions which are palatable and stable when admixed with animal feedstuffs.

The present invention accomplishes these objectives by the provision of novel resinates of N,N-dialkylpiperazine carboxamide compounds having the formula:



where R is hydrogen or C_1-C_6 alkyl and R_1 is alkyl C_1-C_5; and of styrylpyridinium compounds having the formula:



wherein R_2 is C_1-C_4 alkyl and R_3 is hydrogen or halogen.

The above compounds are described in United States Patents 2,467,895 issued April 19, 1949 and 3,177,116 issued April 6, 1965; however, no mention is made by the patentees of resinate forms of said compounds or the improved palatability obtained with said forms.

The resinates of the above-identified compounds are prepared by reacting the free base or pharmacologically acceptable salt of the N,N-dialkylpiperazine carboxamide or the pharmacologically acceptable salt of the styrylpyridinium compound with an acidic cationic exchange resin under conditions whereby said compound becomes ionically bound to the acidic anion of the resin.

The diethylcarbamazine and/or the styrylpyridinium compound is bonded to the resin with sufficient ionic strength to withstand ionization in the mouths of animals. However, the efficacy of these anthelmintic agents is retained since the active compound is released from the resin in the stomach and/or intestinal tract of the animal after being swallowed.

The present invention also provides a palatable anthelmintic composition for warm-blooded animals, the composition comprising the novel resinated N,N-dialkylpiperazine carboxamide of this invention and/or the novel resinated styrylpyridinium compound of this invention, together with an orally acceptable carrier or diluent. Preferably, the carrier includes one or more of the following ingredients: dessicated liver, Brewers yeast, microcrystalline cellulose, stearic acid, sodium aluminum silicate and silicon dioxide. However, it is within the skill of the expert in this art to select other compounding ingredients in the preparation of suitable carriers for the active anthelmintic agents of this invention.

In the most preferred practice of the invention, the novel resinates are admixed with from 18% to 60%

The chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

by weight of desiccated granular or powdered liver, but preferably granular liver; 0% to 40% by weight of Br wers yeast; 23.95% to 31% by weight of microcrystalline cellulose; 7% by weight of stearic acid; 0% to .05% by weight sodium aluminum silicate or silicon dioxide; 2% to 5% by weight of diethylcarbamazine resinate and from 0 to 7% by weight of a styrylpyridinium resinate; said resin employed in the preparation of said resinates having a particle size of less than 800μ and preferably an average particle size between about 45μ and 300μ. Said ion exchange resin being further characteried as a strongly acidic high capacity sulfonic cation exchange resin preferably of the polystyrene divinylbenzene type having from 4 to about 8% cross linkage.

Preferred compositions comprise about 3% by weight of diethylcarbamazine resinate, about 5% by weight of 1 - methyl - 2 - (p - chlorostyryl)pyridinium resinate, about 55% by weight of dessicated liver, about 30% by weight of microcrystalline cellulose, and about 7% by weight of stearic acid. The said resinates being high capacity sulfonic cationic exchange resins of the polystyrene divinylbenzene type with an average particle size in the range of from 45μ to 300μ.

Another preferred composition comprises about 3% by weight of diethylcarbamazine resinate, 5% by weight of 1 - methyl - 2 - (p - chlorostyryl)pyridinium resinate, 18% to 37% by weight of desiccated liver, 37% to 18% Brewers yeast, 30% by weight of microcrystalline cellulose, and 7% by weight of stearic acid.

Still another preferred composition comprises 3% by weight of diethylcarbamazine, 40% by weight of Brewers Yeast, 20% by weight of granular liver, 30% by weight of microcrystalline cellulose, and 7% by weight of stearic acid.

Preparation of the diethylcarbamazine resinate and styrylpyridinium resinate can be achieved by admixing the diethylcarbamazine compound with deionized water or the styrylpyridinium compound with an alcohol-deionized water mixture and intimately contacting the resulting mixture with a high capacity, sulfonic acid cationic exchange resin having a 4% to 8% divinylbenzene cross-linkage and a screen size of about 16 to 50 mesh. The thus prepared resinate is then separated from the supernatant liquid and washed repeatedly with deionized water until the wash water has a pH of about 4.5. The resin is then dried and ground or milled to at least about 800μ and preferably to an average particle size between 45μ and 300μ. The resinates, thus prepared, can be used separately to formulate edible tables or they may be admixed to prepare edible tablets containing both compounds.

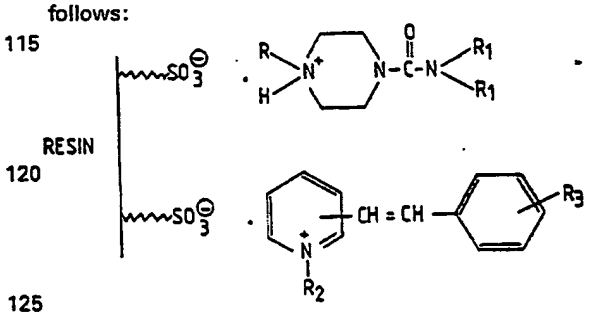
In the preparation of the above-mentioned resinates, alcohols such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, pentanol-1, or pentanol-2, may be employed.

Strongly acidic resins are preferred in the preparation of th resinates of this invention since they provide resinates in which the diethylcarbamazine and/or styrylpyridinium compounds are more strongly bonded to the ion exchange resin to substantially prevent the compounds ionizing in the mouth of the animal to which they are fed. Among the preferred strongly acidic resins are sulfonated polystyrenes prepared from styrene and divinylbenzene which functions as a cross-linking agent. These resins include AMBERLITE® IR-120, and DOWEX® 50 and 50W. Sulfonated phenolic resins, may also be used and may include AMBERLITE® IR-1; cellulose alkylsulfonic acid resins such as CELLEX SE resin and the like may also be utilized in the preparation of the resinates of this invention.

The reaction to form the resinates can be carried out over a wide temperature range so long as the solvent remains fluid and is not evaporated in excessive amounts. For example, the reactions may be conducted at a temperature between about 0° and 100°C and preferably at from about 20° to 50°C.

The diethylcarbamazine or styrylpyridinium solution can be contacted with the resin in any convenient manner such as by mixing the solution with the finely divided resin or by passing the solution of the anthelmintic agent through a resin bed. The molar ratio of anthelmintic agent to resin employed is not critical and is usually within the range of 0.125:1 to 3:1, preferably 0.5:1 to 2:1. A ratio within the preferred range permits efficient loading of the resin within a reasonable period of time. The anthelmintic resinates obtained in accordance with this invention contain about 10% to 60% by weight of anthelmintic and preferably about 40% to 55% of said anthelmintic. The resinate compositions can be prepared by either a batch or a continuous process and if desired both the diethylcarbamazine and styrylpyridinium compound may be loaded on a single resin. However, it is essential that in this arrangement the styrylpyridinium be loaded first and then the loaded resin thoroughly washed before the diethylcarbamazine is loaded on the resin. In this practice the resin is loaded only to about 25% to 33% by weight with the styrylpyridinium, determined on the basis of the dry weight on the resin, and then with about 13% to 18% by weight with diethylcarbamazine, determined on the basis of the dry weight of the resin. The preferred loading ration of styrylpyridinium to diethylcarbamazine or sequentially loaded resins is about 1.7 to 1. However, ratios as low as 1.3 to 1 can be used.

The sequentially loaded resinate, containing both the N,N-dialkylpiperazine carboxamide and the styrylpyridinium compound, may be illustrated as follows:



where R, R_1, R_2 and R_3 are as described above.

Other embodiments and advantages of this invention will become more apparent from the examples set forth below. These examples are provided for the purpose of demonstrating the invention and are not

intend d t limit the scope hereof.

EXAMPLE 1

Preparation of Diethylcarbamazine Resinates and Styrylpyridinium Resinates

Diethylcarbamazine Resinate

Diethylcarbamazine (1125 kg real, 5.653 kg mole) also named N,N-diethyl - 4 - methyl - 1 - piperazinecarboxamide, is charged to 2240 liters of deonized water and agitated to dissolve it. To this solution is then added a high capacity sulfonic cation exchange resin of the polystyrene divinylbenzene type (2380 kg) AMBERLITE IR-120® manufactured by Rohm & Haas Co.. The reaction slurry is filtered, washed with deionized water (2240 liters), and dried at 80°-90°C. The dried diethylcarbamazine resinate (2380 kg) which assays 45.0% diethylcarbamazine free base is then milled to −30 mesh particle size.

The above-mentioned cation exchange resin has a density of 0.85g/cc apparent, 1.26g/cc true; water content 44-48%; exchange capacity of 4.40 milliequivalents /g dry and a screen size of from 16 to 50 mesh.

Styrylpyridinium Resinate

A 3960 gram quantity of a sulfonic acid divinylbenzene resin (H + form) calculated to contain 1500 grams or 7.620 equivalents capacity of dry resin is mixed with a solution containing 2074 grams of 1 - methyl - 2 - (p - chlorostyryl)pyridinium chloride, 3000 ml of methanol and 3900 ml of deionized water. The mixture is diluted to 11,000 ml with deionized water and then allowed to settle and the supernatant liquid separated from the mixture by filtration. This washing treatment is repeated 10 times. The pH of the final wash is 4.50 and the pH of the deionized water is 4.85. The resonate is then dried at 75°C for 48 hours and weighs 2,739 grams. The resinate passes through a 20 mesh screen and assays 52.38% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium as the chloride and has a KF moisture content of 1.305%. The resin used in the above preparation is marketed under the tradename Powdex by the Graver Water Conditioning Co., N.Y., N.Y. and is essentially 20-50 mesh material.

EXAMPLE 2

Preparation of Diethylcarbamazine Resinate

A mixture of 20-50 mesh washed Powdex resin (1667g wet resin, calculated to contain 698.0g dry resin or 3.546 equivalents capacity) and 500 ml of deionized water are mixed in a vessel. To this mixture is added 719.28 (706.6g, real; 3.546 moles) of diethylcarbamazine base. The mixture is stirred for 4 hours and then filtered and washed repeatedly with deionized water. The resinate is collected and dried at 85°C for 24 hours. The dried resinate weighs 1389g and assays 50.59% and 50.30% diethylcarbamazine base.

EXAMPLE 3

Preparation of Diethylcarbamazine Resinate-Edible Tablets

Diethylcarbamazine resinate (71.28kg 3.24% w/w) pr pared in accordance with the procedure of Example 1 above is blended with 1.10 kg f colloidal silicon dioxide. Brewers yeast 873.62 kg (39.71% w/w) is passed through a 30 mesh screen and blended with the prepared diethylcarbamazin mixture. The resulting mixture is then admixed with 660.00 kg of microcrystalline cellulose. The mixture is passed through a 30 mesh screen, blended with 154.00 kg of stearic acid, 440.00 kg of dessiccated, granular, liver (20% w/w) and compacted into 2.20 g tablets using a commercial tableting machine.

EXAMPLE 4

Preparation of Diethylcarbamazine Resinate-Edible Tablets

Diethylcarbamazine resinate (71.2 kg 3.24% w/w) prepared in accordance with example 3 is admixed with 0.44 kg of sodium aluminum silicate. Desiccated, powdered, liver 444.0 kg 20.0% w/w) is then passed through a 30 mesh screen and blended with the previously prepared resinate mixture and to this mixture is added 874.28 kg (34.94% w/w) of Brewers yeast, 660.00 kg of microcrystalline cellulose and 1540.00 kg of stearic acid. The thus prepared mixture is thoroughly blended and then formed into 2.20 g tablets using a commercial tableting machine.

EXAMPLE 5

Preparation of diethylcarbamazine resinate — styrylpyridinium resinate edible tablets

Diethylcarbamazine resinate (71.28 kg 3.24% w/w) and 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate (104.94 kg 4.77% w/w) prepared in accordance with Example 1 are blended with 1.1 kg of colloidal silicon dioxide. Desiccated-granular liver (440.0 kg 20.0% w/w) is screened through a 30 mesh screen and admixed with the resinate mixture. Brewers yeast (768.68 kg) 34.94% w/w) is then passed through a 30 mesh screen and mixed with the previously prepared resinate mixture. Microcrystalline cellulose (660.00 kg) and 154.00 kg of stearic acid are blended with the above-noted mixture and the resulting formulation formed into 2.2 g tablets using a commercial tableting machine.

EXAMPLE 6

Palatability Evaluation of Styrylpyridinium Diethylcarbamazine edible tablets

The following tests are conducted to determine comparative acceptabliity of various acceptability of various formulations of tablets containing 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate and diethylcarbamazine resinate.

Twenty adult purebred English Pointers are used in these evaluations. The dogs are housed individually in outside pens. Each pen is 4 feet wide, 10 feet long and is provided with an attached house. Poinsters are used for this test because of their organoleptic sensitivity to differences between products.

Each dog is tested for intestinal parasites by a flotation method using sodium nitrate solution and Fecasol® kits. Dog 7 is found to have a slight infestation of *Toxascaris leonina* and Dog 12 a ruminant parasite. Both infestations are gone after 14 days.

Tests for Dirofilariasis are conducted using Knott's technique and all blood samples are free of microfilaria.

In the tests each dog is fed, *ad libitum,* commercial dry dog food in self-feeders, and fresh, clean, water is available at all times.

A double choice format is employed with each dog being offered two choices of tablet formulations simultaneously to determine acceptability prefer-

ences.

The feeding containers used are rectangular plywood sheets, 30 by 31 cm, 2 cm thick, with routed depressions 3.7 cm in diameter and 1.1 cm deep.

Each dog is offered two tablets each morning and again in the afternoon for four days. Presentation is alternated each time by turning the containers 180° before placing it in the cage. Time acceptance is noted for each proffering. The container is left in the cage 30 minutes if the tablets are not readily consumed.

All dogs are less than 4 years of age and weigh between 35 and 52 pounds. The sex, habitus and initial and final weights of each dog are recorded and reported below. Also reported are the findings obtained in this test along with formulation used.

Table I
English Pointers used in this test

Pen	*Sex*	*Habitus*	*Initial weight lbs.*	*Final weight lbs.*
1	F	muscular	48	43
2	F	light	35	43
3	F	light	38	35.5
4	F	muscular	49	46
5	F	light	37	35.5
6	F	fat	49	47.5
7	F	light	39	39
8	F	average	41.5	43
9	F	muscular	46	42.5
10	F	light	40.5	40
11	M	average	45	42.5
12	F	fat	49.5	50
13	M	muscular	52	50
14	F	light	37	36
15	M	muscular	52.5	50.5
16	F	average	40	39
17	M	muscular	50	50.5
18	F	light	37	38.5
19	F	average	45	43
20	F	light	38	38.5

First Preference Test Results for Styrylpyridinium-Diethylcarbamazine Resinate Tablets

Comparisons:		A	B	B	C	A	D	B	E	F	G	G	H
Dog #	1	2	3	7	2	8	1	8	2	5	5	3	7
	2	3	6	6	3	4	5	6	4	5	5	4	6
	3	5	5	7	3	7	3	10	0	5	4	3	7
	4	2	8	7	3	7	3	4	6	2	8	6	4
	5	3	6	5	5	5	5	1	9	3	7	4	6
	6	7	3	8	2	5	5	6	4	6	4	5	5
	7	4	6	4	6	9	1	5	5	6	4	5	5
	8	5	5	7	3	8	2	7	3	6	4	4	6
	9	4	6	5	5	10	0	6	4	5	5	6	4
	10	5	5	5	5	6	4	5	5	5	5	6	4
	11	4	6	7	3	8	2	4	6	4	6	5	5
	12	3	7	4	6	7	3	6	4	5	5	7	3
	13	6	4	4	6	5	5	5	5	6	4	5	5
	14	2	8	4	6	7	3	5	5	7	3	4	6
	15	6	4	5	5	7	3	8	2	2	7	7	2
	16	5	5	6	4	5	5	5	5	5	5	5	5
	17	5	5	6	4	4	6	8	2	6	0	2	3
	18	4	6	5	5	6	3	5	5	6	4	7	3
	19	6	4	4	6	10	0	8	2	4	6	7	3
	20	4	6	6	4	9	1	6	4	6	4	3	7
Totals: Selected First)		85	108	112	86	137	60	118	82	99	95	98	96

Tablet Compositions % w/w

A = 36.36% Desiccated liver
18.18% Brewers yeast
30.67% Microcrystalline cellulose
2.92% Diethylcarbamazine resinate
7.00% Stearic acid
4.87% 1 - methyl - 2 -, (p - chlorostyryl) - pyridinium resinate
Resinate particle size 300-800μ
4% Sulfonic acid-divinylbenzene cross linkage

B = 54.55% Desiccated liver
30.66% Microcrystallin cellul se
4.87% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate
2.92% Diethylcarbamazine resinate
7.00% Stearic acid
Resin particle size 300-800μ
4% Sulfonic acid-divinylbenzene cross linkag

C = 36.36% Brewers yeast
18.18% Desiccated liver
30.67% Mycrocrystalline Cellulose
4.87% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate
2.92% Diethylcarbamazine resinate
7.00 Stearic acid
Resin particle size 300-800μ
4% Sulfonic acid-divinylbenzene cross linkage

D = Filarabits – Commercial edible formulation of Diethylcarbamazine

E = 36.36% Brewers yeast
18.18% Desiccated powd red liver
5.19% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate
3.01% Diethylcarbamazine resinate
30.26% Microcrystalline cellulose
7.00% Stearic acid

Resin particle size 147-300μ,
4% Sulfonic acid-divinylbenz ne cross linkage
F = 35.8% Br wers yeast
18.0% Desiccated powdered liver
5.97% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate
3.18% Diethylcarbamazine resinate
0.05% Colloidial Silicon Dioxide
30.00% Microcrystalline cellulose
7.00% Stearic acid
Resin particle size 147-300μ,
4% Sulfonic acid-divinylbenzene cross linkage
G = 36.77% Brewers yeast
18.0% Desiccated powdered, liver
5.28% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate
2.95% Diethylcarbamazine resinate
30.00% Microcrystalline cellulose
7.00% Stearic acid
Resin particle size <147μ,
8% Sulfonic acid-divinylbenzene cross linkage
H = 36.52% Brewers yeast
18.00% Desiccated powdered, liver
5.30% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate
3.18% Diethylcarbamazine resinate
30.00% Microcrystalline cellulose
7.00% Stearic acid
Average resin particle size 45μ
4% Sulfonic acid-divinylbenzene cross linkage

From the above data it can be seen that formulation B, which contains approximately 55% by weight of liver, is most aggressively accepted by dogs. Formulation A, containing approximately 18% by weight of Brewers yeast and 40% by weight of liver is the next most palatable formulation, and formulation C, containing about 18% by weight of liver and 40% by weight of Brewers yeast is the third most palatable formulation to the dogs. All these formulations were most palatable than the commercial Filarabit (diethylcarbamazine) formulation. Formulation F, G and H were all readily acceptable to the test dogs and were equivalent in palatability ratings. In all cases, most dogs ate both tablets as treats within 1 minute. The use of about 20% liver or more improves the rate of acceptance primarily by beneficial olfactory stimulation.

EXAMPLE 7

Palatability evaluation of styrylpyridinium - diethylcarbamazine edible tablets

The test described in example 6 above is repeated using 20 to 60 pound mongrel dogs. Tablets A, B, C and D, described in example 6, are evaluated in this test along with three different formulations designated I, J and K. The latter formulations have the following compositions:

I = 18.18% Desiccated liver powder
36.36% Brewers yeast
30.10% Monocrystalline cellulose
5.28% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate
3.08% Diethylcarbamazine citrate (no resin)
7.00% Stearic acid
J = 46.36% Brewers yeast
8.18% Desiccated liver powder
30.49% Monocrystallin cellulose
5.05% 1 - methyl - 2 - (p - chl rostyryl) - pyridinium resinate
2.92% Diethylcarbamazin r sinate
7.00% Stearic acid
K = 54.54% Brewers yeast
30.49% Monocrystalline cellulose
5.05% 1 - methyl - 2 - (p - chlorostyryl) - pyridinium resinate
2.92% Diethylcarbamazine resinate
7.00% Stearic acid

As in example 6, the tablets are offered to each dog twice daily for five days. Preference for formulations is reported as % consumed first.

First Preference test Results
Styrylpyridinium-Diethylcarbamazine formulations

Formulation	*% liver*	*% yeast*	*% consumed first*
A	36.36	18.18	56.4
C	18.18	36.36	43.6
A	36.36	18.18	41.0
B	54.55	0	59.0
B	54.55	0	66.0
D (Filaribits)	—	—	34.0
C	18.18	36.36	67.0
I = Nonresinated Diethylcarbamazine Styrylpyridinium resinate	18.18	36.36	33.0
J	8.18	46.36	56
K	0	54.54	44

From the above data it can be seen that the formulation prepared with about 54.55% liver was the most preferred formulation, However, formulations A, B and C, were all acceptable and preferred over the commercial "Filaribits" diethylcarbamazine formulation. Thus it is apparent that styrylpyridinium resinate-diethylcarbamazine resinate formulations containing 20% to 60% by weight of liver and 0-40% by weight of yeast are more acceptable i.e. palatable to dogs than the presently offered commercial preparations. The formulation containing non-resinated diethylcarbamazine was not well accepted nor were the formulations containing 0 to 9% by weight of liver.

EXAMPLE 8

Palatability Evaluation of Styrylpyridinium Diethylcarbamazine edible tablets

Twenty-five to 29 privately-owned pet dogs representing a variety of ages, bodyweights, breeds and both s x s were used in a series of 3 day acceptanc studies. STYRID-CARICIDE Tablets to provid therapeutic levels f styrylpyridinium and diethylcarbamazine for a 20lb. dog were formulat d with a variety of liv r contents and resinated or non resinated active drug components. The formulation

used (A thru K) were specified in Examples 6 and 7 as follows:

Formulation	% Liver	% Yeast	Drugs
A	36.36	18.18	CARICIDE Resinate STYRID Resinate
B	54.55	0	CARICIDE Resinate STYRID Resinate
C	18.18	36.36	CARICIDE Resinate STYRID Resinate
I	18.18	36.36	CARICIDE Citrate STYRID Resinate
J	8.18	46.36	CARICIDE Resinate STYRID Resinate
K	0	54.54	CARICIDE Resinate STYRID Resinate

One additional formulation to be designated formulation "L" using about 20% liver, 40% yeast with

* Styrylpyridinium = STYRID
* Diethylcarbamazine = CARICIDE

CARICIDE resinate as the only active drug was also evaulated as was Diroform ®, an edible formulation of diethylcarbamazine made by Vet-A-Mix, Inc., Shenandoah, Iowa.

Whole or parts of tablets were offered free-choice appropriate to the individual dogs body weight once daily for 3 consecutive days. A period of about 2 weeks separated each 3 day test. Acceptance of each formulation was calculated at the percentage of the total number of daily tablet presentations which were readily consumed by the dogs. If less than the entire daily dosage was accepted, then that day was considered a rejection of medication. Results are listed below:

Formulation	% Liver	% Yeast	% Acceptance
K	0	54.54	61
J	8.18	46.36	80
C	18.18	36.36	96
A	36.36	18.18	96
B	54.55	0	96
I	18.18	36.36	76
L	about 20	about 40	89
Diroform	—	—	79

All results were made using a resin of 300-800μ particle size with 4% divinylbenzene cross linkage. An excellent acceptance was attained with liver present at a concentration of about 20% or greater. Relatively poor acceptance was observed at about 10% or less liver content. A relatively low acceptance rate was seen for the now resinated diethylcarbamazine formulation (I) which was nearly equivalent to that observed for Diroform a potentially competitive product. When diethylcarbamazine resinate alone was incorporated into the 20% liver matrix it compared very favorably with the non-resinated diethylcarbamazine formulation.

EXAMPLE 9

Sequentially Loaded Styrylpyridinium - Diethylcarbamazine Resin

DOWEX ® 50W, sulfonated polystyren - divinylbenzene cross-linked acidic resin, 3000g is placed in a 10 l. graduated cylinder. Styrylpyridinium chloride (510.5g) is then dissolved in 1200ml f deionized water and 300ml of methanol and added to the DOWEX 50W resin. The mixture is stirr d for 2 hours and then permitted to settle and the acidic supernatant liquid decanted. The remaining styrylpyridinium resinate is washed 3 times with deionized water, then permitted to settle and the supernatant liquid separated from the resinate. Diethylcarbamazine base (306.3g) is then added to the resinate and sufficient deionized water added to adjust the volume of the mixture to 11l. The resulting mixture is stirred for 2 hours until the diethylcarbamazine is loaded on the resin along with the styrylpyridinium. The mixture is washed several times and until the final wash and resin mixture has a pH of 4.30. The supernatant liquid is separated from the styrylpyridinium-diethylcarbamazine resinate which is then dried and ready for use in preparation of the edible tablets.

The above procedures are repeated using POWDEX Resin (IR 120) ground to 45μ (2820g). The styrylpyridinium chloride (501.g) is the first drug to be loaded on the resin as described above. This is accomplished in a methanol water solution. The resin is washed three times with deionized water and the supernatant liquid decanted. Diethylcarbamazine (291.g) is then sequentially loaded onto the washed styrylpyridinium resinate and stirred for 17 hours. The mixture is permitted to settle, the supernatant liquid decanted and the remaining resinate washed with deionized water until the pH of the wash water mixture is about 1.7.

EXAMPLE 10

Preparation of Styrylpyridinium - Diethylcarbamazine edible tablets using sequentially loaded resin

Styrylpyridinium - diethylcarbamazine sequentially loaded resinate (355.4g) is admixed with 800g of desiccated powdered liver, 1200g of microcrystalline cellulose (AVICEL PH102); 1362.6g of Brewers yeast; 2.0g of silicon dioxide and 280.g of stearic acid. The composition, thus prepared, contained 8.885% by weight of the resinated drug, 20% by weight of liver, 30% by weight of microcrystalline cellulose, 34.065% by weight of the yeast, 0.05% by weight of the silicon dioxide and 7.0% by weight of the stearic acid.

The composition is compressed into chewable 2.2g tablets having a Kilopond hardness rating of about 8.5 Kp. The palatability of the thus prepared tablets is excellent.

EXAMPLE 11

Diethylcarbamazine Edible Tablet Palatability Evaluations using privately owned dogs maintained under Home Environment Conditions

In this study, heartwarm (*Dirofilaria immitis*) negative dogs representing a random variety of breeds, ages, body weights, and both sexes, are offered diethylcarbamazine edible tablets prepared as described in example 3 above. The medicated edible tablets were offered to each dog once a day for 30 consecutive days.

Each dog is rated according to the number of acceptance as a percentage of the total number f daily presentations using the following classifications criteria:

Rating	*Acceptance*
Excellent	Accepted 90% or more of the daily doses
Good	Accepted 89% to 75% of the daily doses
Fair	Accepted 74% to 51% of the daily doses
Poor	Accepted 50% or less of the daily doses

Tablets are presented at the owner's convenience, usually prior to or during a meal. The acceptability panel was made up of 37 dogs representing a random variety of breeds, both sexes, a body weight range of 4.5 to 55.4 kg, and an age range of 6 months to 12.5 years as shown in table I. Acceptability results are shown in Table II, and are summarized below:

Rating	*Number of Dogs*	*% of Total Panel*
Excellent	30	81
Good	2	5
Fair	0	0
Poor	5	14

"Excellent" to "Good" acceptance was observed for 86% of the panel members and "Fair" to "Poor" acceptance for 14% of the panel. In general, acceptance or rejection of the tablets was not a function of the method of administration, i.e. as a treat vs. mixed with food. If the tablets were consistently rejected, the test, while still reported, was terminated for that individual prior to completion of the full test period. Throughout the trial, only one dog, was "sick". This occurred on the twenty-first day of medication and lasted for one day only. This dog was continued on medication for an additional 12 days (total of 42 days of treatment), with no adverse effects noted. Two of the smaller dogs preferred the tablets broken into pieces, but when broken, accepted them well.

TABLE I
Acceptability Panel Composition

Breed	*Males*	*Females*	*Age (Range)*	*Body Weight (Range in kg)*
Borzoi	1	1	2.5 - 3.5 yr.	31.5 - 55.5
Collie		1	13 months	27.5
Dachshund	1	3	3 - 10 years	6.0 - 8.0
German Shepherd		1	2.5 years	29.5
G.S.H. Pointer		1	6 months	18.0
Golden Retriever		2	1.5 - 6 years	29.5 - 32.0
Irish Setter	1		8 months	27.5
Labrador Retriever	1	2	11 months - 5 years	31.0 - 36.5
Miniature Poodle		1	12.5 years	8.0
Miniature Schnauzer	3	2	1 - 10 years	4.5 - 9.0
Shetland Sheepdog	1		1.5 years	7.0
Standard Poodle		1	3 years	26.0
Welch Corgi	2	3	5 - 11 years	7.5 - 13.5
West Highland White Terrier	1		2 years	8.5
Mixed	4	4	1.5 - 8 years	8.5 - 45.5
Totals	15	22	Range: 6 months to 12.5 years	Range: 4.5 to 55.4 kg

TABLE II
Dog Acceptance Information and Owners Comments

Dog			Days Accepted	Days Rejected	% of Presentations Accepted	How Given	Comments
Breed	Age	Sex[1]					
Irish Setter	8 mo.	M	30	0	100	Treat	Loved it
German Shepherd	2.5 yr.	F	45	0	100	Treat	Ate it
Schnauzer	1 yr.	F	31	0	100	Treat	Quick Acceptance
Schnauzer	7 yr.	M	31	0	100	Treat	Quick Acceptance
Schnauzer	10 yr.	M	27	4	87	Treat	Occasionally crumbled prior to presentation
Schnauzer	5 yr.	M	24	7	77	Treat	Occasionally crumbled tablet or combined with food

TABLE II (Continued)
Dog Acceptance Information and Owners Comments

Dog			Days Accepted	Days Rejected	% of Presentations Accepted	How Given	Comments
Breed	Age	Sex					
Dachshund	7 yr.	F	31	0	100	Treat or with food	None
Dachshund	10 yr.	F	31	0	100	Treat or with food	None
Golden Retriever	1.5 yr.	F	31	0	100	Treat or with food	None
Golden Retriever	6 yr.	F	25	1	96	Treat	Excellent
W.H.W. Terrier	2 yr.	M	29	2	94	Treat or with food	Good
Miniature Poodle	12.5 yr.	F	30	1	97	Treat	Well accepted
Standard Poodle	3 yr.	F	31	0	100	Treat	Well accepted
Mix	8 yr.	F	0	3	0	Treat or with food	None
Dachshund	4 yr.	F	30	0	100	Treat	None

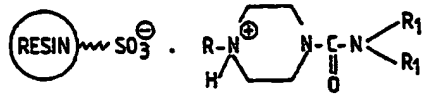
Edible Tablet Composition

	Ingredient	*% Composition*
1.	Diethylcarbamazine Resinate*	3.063
2.	Silicon dioxide, colloidal	0.05
3.	Brewer's Yeast	39.887
4.	Cellulose, microcrystalline	30.0
5.	Stearic Acid, powder USP	7.0
6.	Liver, dessicated (granular)	20.0
	Total:	100.0%

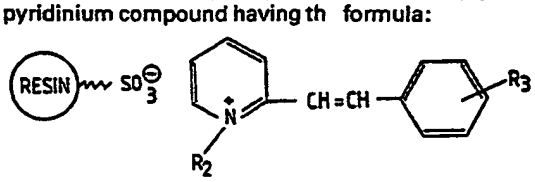
Mean tablet weight: 2.232 g.
Assay: 2.75% w/w as DEC citrate

CLAIMS

1. A palatable anthelmintic resinate composition comprising from 2% to 5% by weight of a resinated N,N-dialkylpiperazine carboxamide compound having the formula:



where R is hydrogen or alkyl C_1-C_6 and R_1 is alkyl C_1-C_5; from 0 to 7% by weight of a resinated styryl-pyridinium compound having the formula:



where R_2 is alkyl C_1-C_4, R_3 is hydrogen or halogen; 18% to 60% by weight of desiccated liver; 0 to 40% by weight of Brewers yeast; 23.95% to 31% by weight of microcrystalline cellulose, 7% by weight of stearic acid; and 0% to 0.05% by weight of sodium aluminum silicate or silicon dioxide.

2. The composition according to Claim 1 wherein the N,N-dialkylpiperazine carboxamide is diethylcarbamazine and is present in the composition in the amount of 3% by weight as the resinate, the styrylpyridinium compound is 1 - methyl - 2 - (p - chlorostyryl)pyridinium resinate and is present in the composition in the amount of 5% by weight; the desiccated liver is 18% to 37% by weight of the composition, Brewers yeast is 37% to 18% by weight of the composition; microcrystalline cellulose is 30% by weight of said composition and stearic acid is 7% by weight of said composition.

3. The composition according to Claim 1, wherein said composition comprises about 3% by weight of diethylcarbamazine resin; 5% by weight of 1 - methyl - 2 - (p - chlorostyryl)pyridinium resin; 55% by weight of desiccated liver; 30% by weight of microcrystalline cellulose; and 7% by weight of stearic acid.

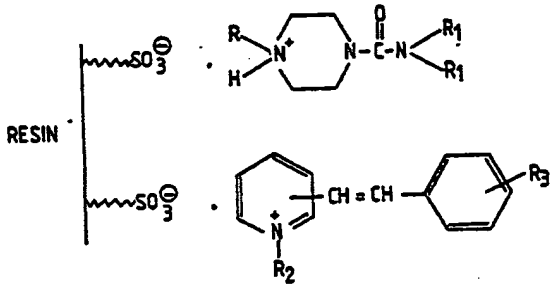
4. The composition according to any preceding claim, wherein the resin is a high capacity sulfonic cationic exchange resin of the polystyrene-divinylbenzene type having a particle size of less than 800μ.

5. The composition according to Claim 4, wherein the resin has an average particl size range between 45μ and 300μ.

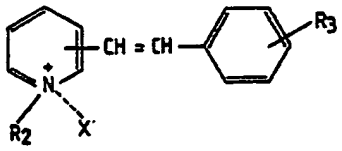
6. The composition according to any preceding claim, wherein said composition is formed into a chewable tablet for administration to companion animals.

7. A palatable, chewable, anthelmintic tablet comprising from 2% to 5% by weight of diethylcarbamazine resinate; from 18% to 60% by weight of desiccated liver; from 0 to 40% by weight of Brewers yeast; 23.95 to 31% by weight of microcrystalline cellulose; 7% stearic acid and from 0 to 0.05% of sodium aluminum silicate or silicon dioxide.

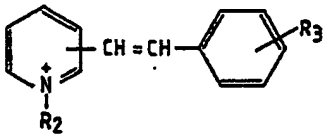
8. A method for the preparation of a sequentially loaded, medicated cationic exchange resin having the formula:



wherein R is hydrogen or C_1-C_6 alkyl; R_1 is C_1-C_5 alkyl; R_2 is C_1-C_4 alkyl; R_3 is hydrogen or halogen and the resin is a high capacity, sulfonic acid, cationic exchange resin, comprising; reaction a styryl-pyridinium compound having the formula:



where in R_2 and R_3 are as described and X is a pharmacologically acceptable anion, dissolved in an aqueous solution of deionized water and a lower alkyl C_1-C_4 alcohol, with a high capacity, sulfonic acid, cationic exchange resin until said resin is loaded to about 25% to 33% by weight with a stypyridinium compound of the structure:



where R_2 and R_3 are as described above; separating the aqueous alcoholic solution from the loaded resin and washing the loaded resin with dei nized wat r until the pH of th wash wat r-resin mixture is 4.30 or bel w; separating said wash water from said resin and reacting the partially loaded styrylpyridinium-resin with n aqueous solution containing from 15% to 21% by weight f diethylcarbamazine, determined on th basis f dry resin, until said partially loaded resin is loaded with from 15% to 21% by weight of diethylcarbamazine, thereaft r separating the aqueous solution from the loaded resin, washing said resin with deionized water, separating said wash water from said resin and recovering the desired sequentially resin.

9. A method according to claim 8 wherein said resin has a loading capacity of about 5 milli-equivalents per gram dry weight of resin and the styrylpyridinium to diethylcarbamazine loading ratio is about 1.67 to 1.

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